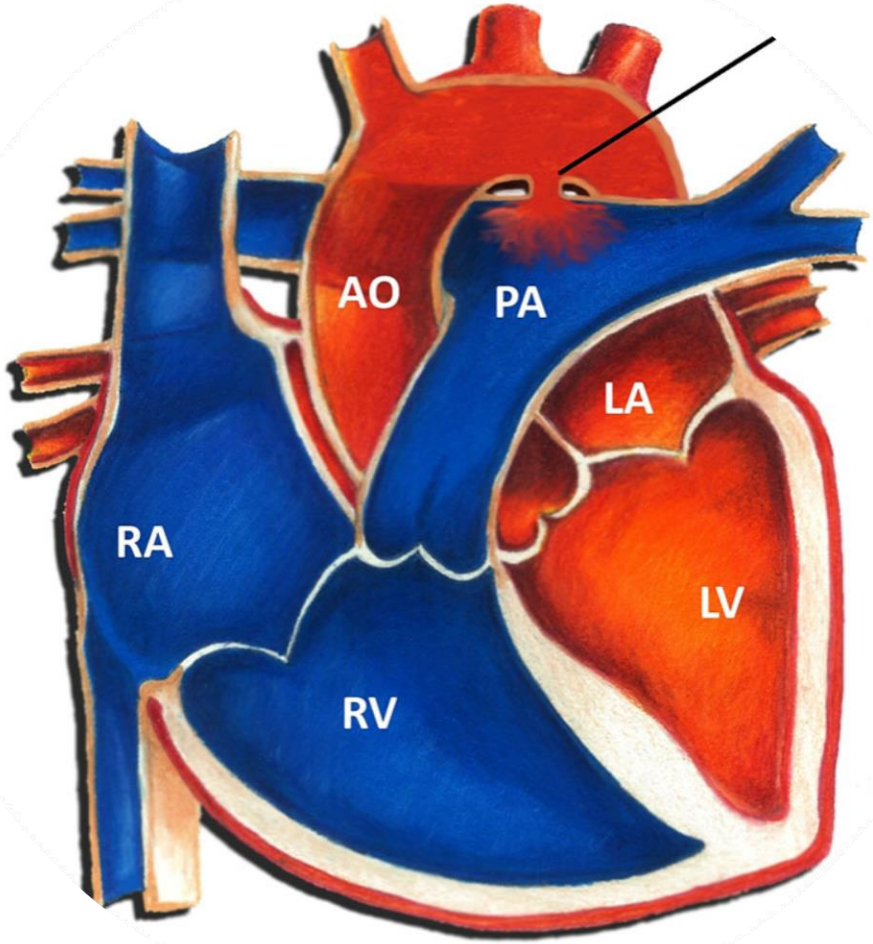
وزارة الصحة
Ministry of Health
مدينة الملك فهد الطبية
King Fahad Medical City

The PDA:

Leave It or Treat It?

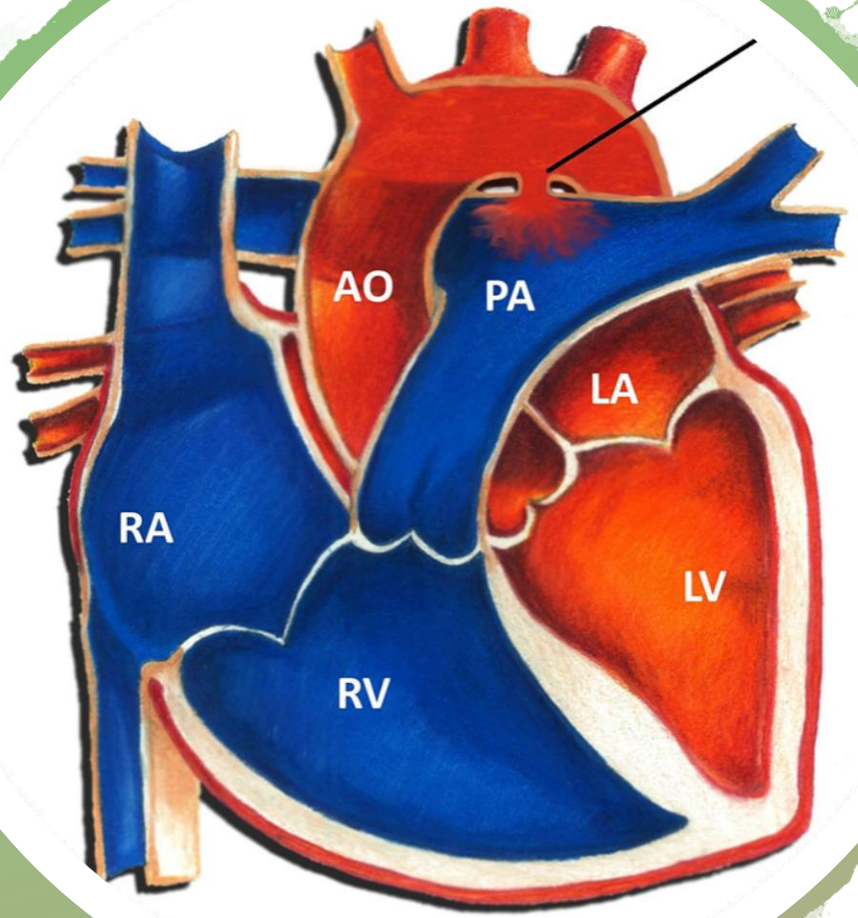


Dr. Omar Elkhateeb
Consultant Neonatologist
King Fahad Medical City

November 26, 2018
Saudi Neonatology Society

Saudi Neonatology Society

Objectives



- Case presentations
- The Anatomy & Physiology of the PDA
- Timing of Closure
- Complications of PDA
- Management of PDA
- Conclusions & Take Home Message
- Questions

Case 1:

- 27 weeks, 850 grams male. RDS. Surf x1
- G2P1 29 yo Mom. C-section due to PET.
- On Day6: Still intubated +Murmur
- Echo: Large PDA, L to R shunt. LA/Ao=1.7
- Feeds 1 ml q2
- FiO2 0.33. BP 46/18 mean 26. U.O 1.5.
- Leave the PDA or Treat it??

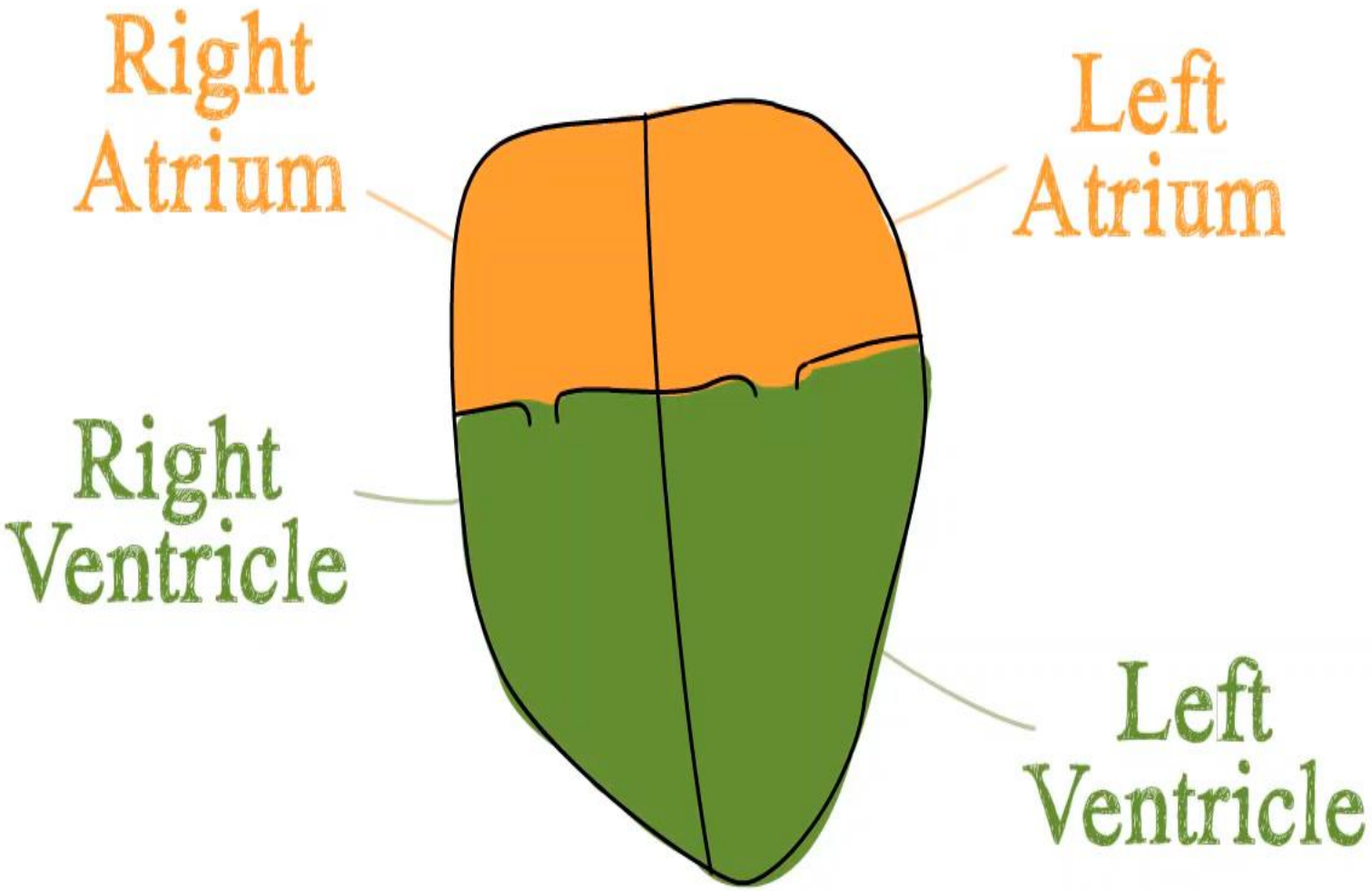
Case 2:

- 24 wk, 590g
- Mom 30 yo, primigravida, antenatal steroids x2, 24h ago
- Preterm labour and delivery
- Surf, ventilation
- Day 0:

  Indo prophylaxis: yes or no?

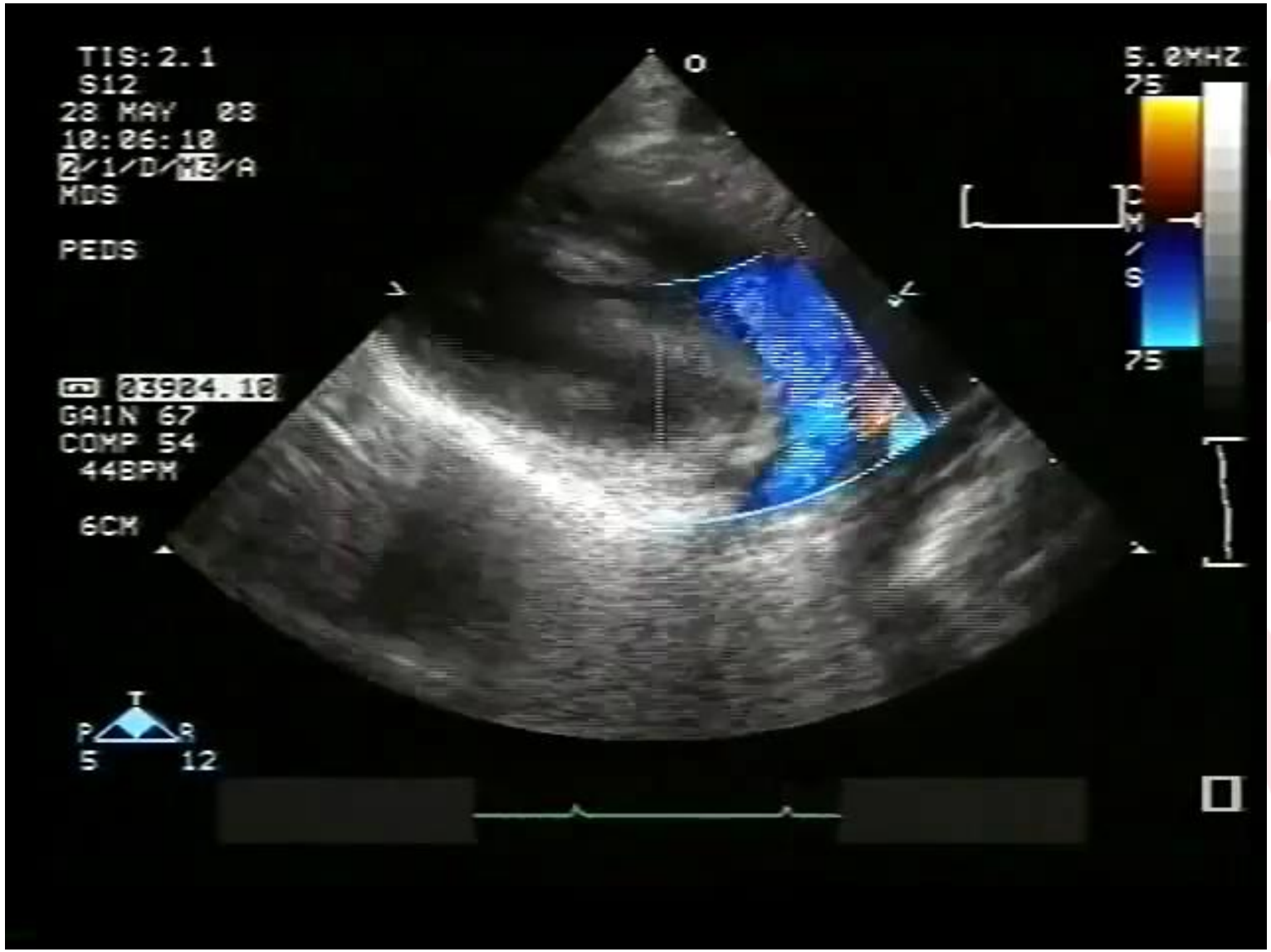
وزارة الصحة
Ministry of Health
مدينة الملك فهد الطبية
King Fahad Medical City

Video

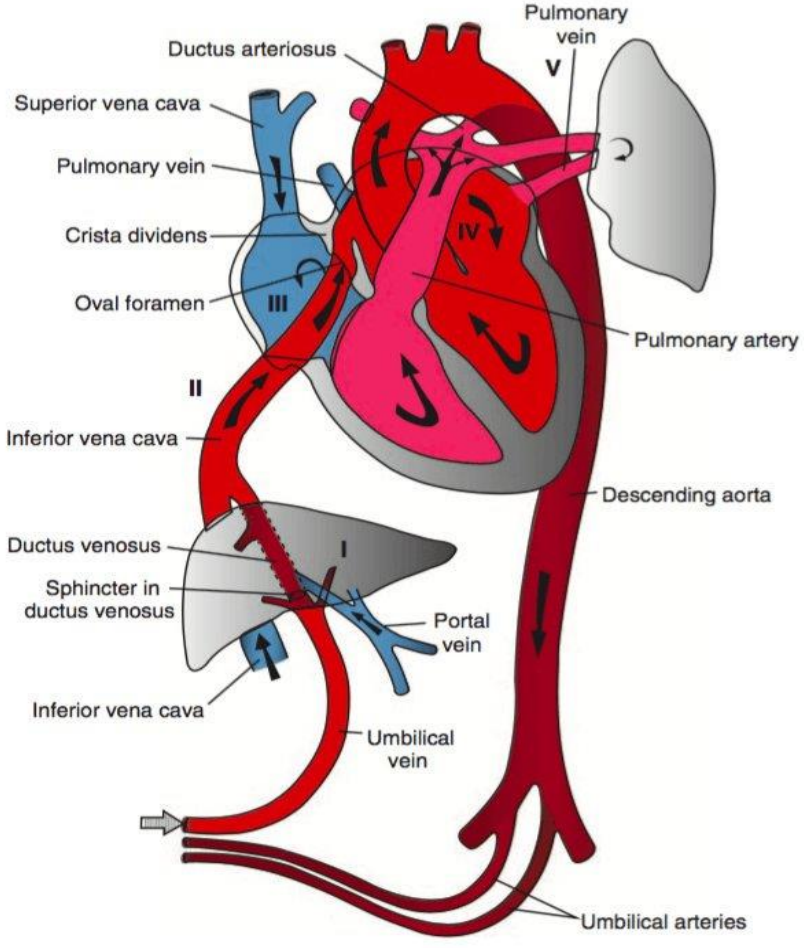


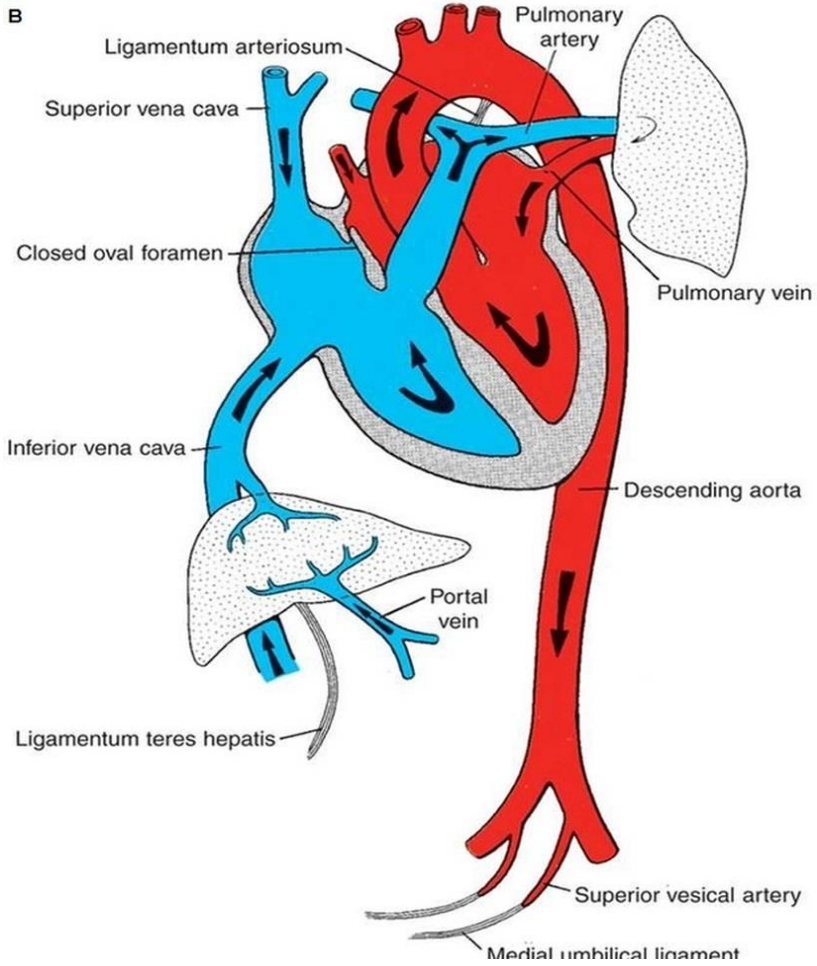
وزارة الصحة
Ministry of Health
مدينة الملك فهد الطبية
King Fahad Medical City

ECHO Video



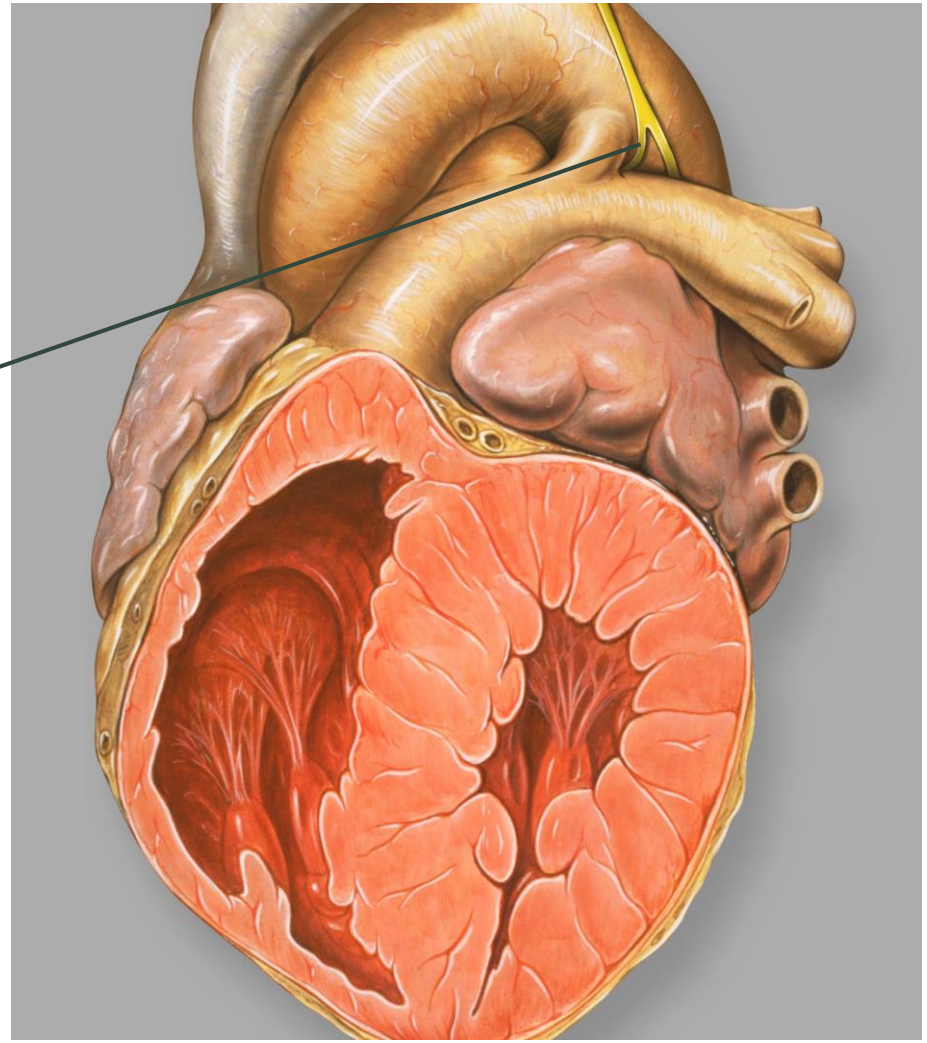
Circulation: From Fetal to Neonatal



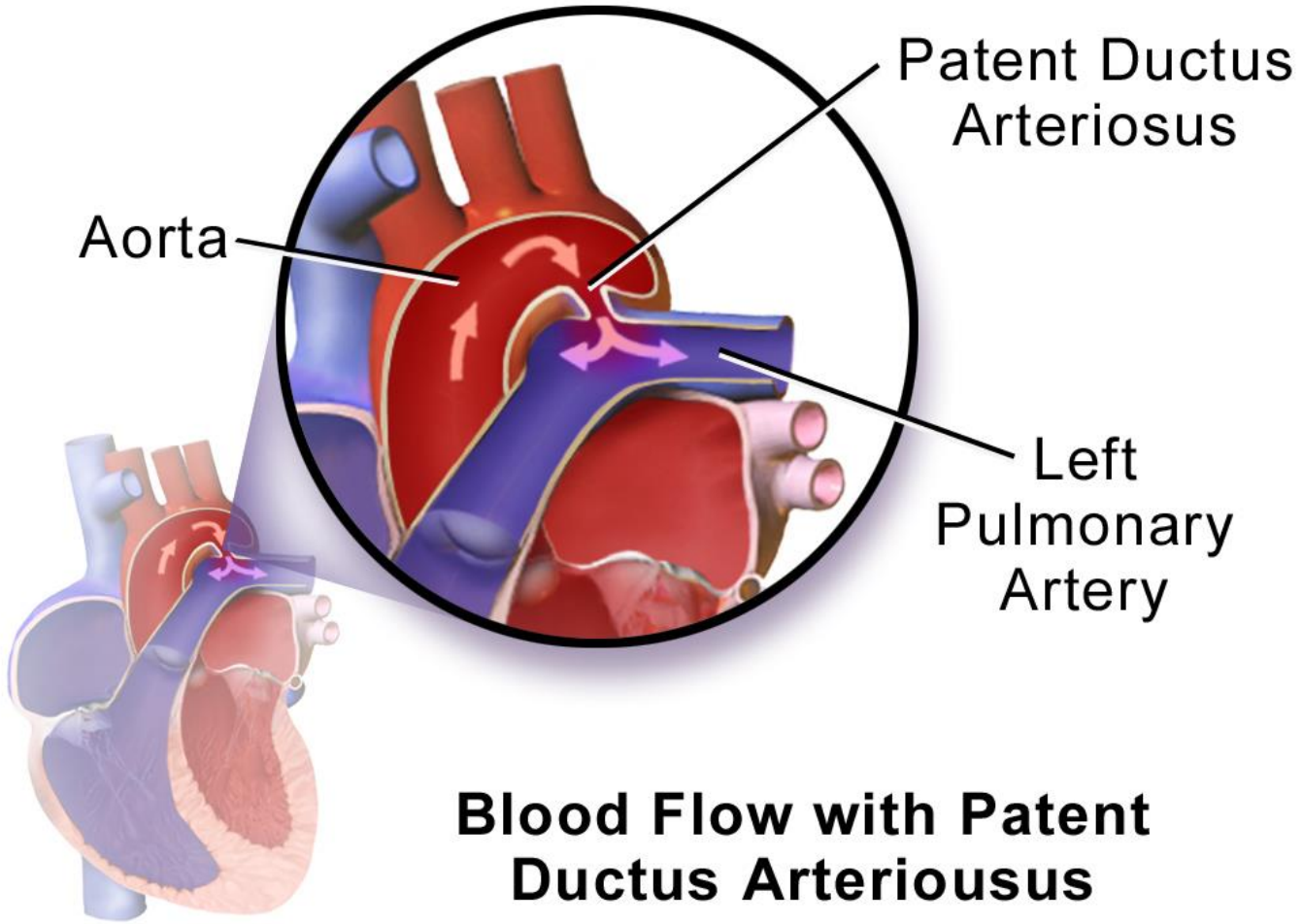


وزارة الصحة
Ministry of Health
مدينة الملك فهد الطبية
King Fahad Medical City

Anatomical Proximity to the Recurrent Laryngeal Nerve



Blood Flow through the PDA



Blood Flow with Patent Ductus Arteriousus

PDA Closure Rates

- **Term:** Functional closure by 72h

- **Preterm:** open at 4 days of age in:
  - 10% of infants born at 30-37 wk (2% at 7 days)
  - 80% of those born at 25-29 wk (65% at 7 days)
  - 90% of those born at 23-24 wk (87% at 7 days)

- closes without treatment in infants >28 wk (73%) & in those with BW >1000 g (94%)

Clyman RI, Couto J, Murphy GM. Patent ductus arteriosus: are current neonatal treatment options better or worse than no treatment at all? *Semin Perinatol.* 2012;36(2):123–129

وزارة الصحة
Ministry of Health
مدينة الملك فهد الطبية
King Fahad Medical City

Mechanism of Closure

- PGs (from placenta), & low PO2 control ductal patency in utero
- After delivery, PO2 rises⟶ rapid muscular constriction
- Lungs eliminate circulating PGs ⟶ further constriction
- Intense contraction ⟶ ischemia ⟶ necrosis, obliterating any ductal shunting
- Functional closure occurs within the first 24 hours, followed by anatomic tissue remodeling within few months

Why is closure delayed in preemies?

- Preterm ductal tissue has ↓ O2 sensitivity, ↑ PG sensitivity

- No sufficient hypoxia in the ductal tissue → anatomic closure will not occur

وزارة الصحة
Ministry of Health
مدينة الملك فهد الطبية
King Fahad Medical City

Associations with the PDA

- feeding intolerance
- NEC
- metabolic acidosis
- renal failure
- IVH
- pulmonary hemorrhage
- CLD
- 4- to 7-fold increase in death

McNamara PJ, Sehgal A. Towards rational management of the ductus arteriosus: the need for disease staging. *Arch Dis Child Fetal Neonatal Ed*. 2007;92:F424-F427. doi:10.1136/adc.2007.118117

وزارة الصحة
Ministry of Health
مدينة الملك فهد الطبية
King Fahad Medical City

PDA In Literature

- More than 68 trials with about 5000 infants
- Thousands of retrospective studies delineating association with poor outcomes
- 43 times mentioned in Cochrane Review
- More than 25 systematic reviews
- Indo, Ibuprofen, Paracetamol, ligation, early, vs late
- Not one study on treating vs no treatment at all

Assessment of the hsPDA

Limrungsikul 2011: What's hsPDA?

surveyed 659 neonatologists & 287 pediatric cardiologists

Most commonly: worsening blood gas, cardiomegaly on chest radiograph, wide PP, low BP, oliguria, pH, murmur, & feeding intolerance

a wide variation among neonatologists & cardiologists when diagnosing hsPDA based on ECHO criteria

The most common practice is to assess ductal size, although it varies with O2, surfactant & furosemide exposure

Zonnenberg 2012: What's a hsPDA?

ACTA PÆDIATRICA
NURTURING THE CHILD

Acta Pædiatrica ISSN 0803–5253

REGULAR ARTICLE

The definition of a haemodynamic significant duct in randomized controlled trials: a systematic literature review

Inge Zonnenberg (koert.dewaal@hnehealth.nsw.gov.au)[1], Koert de Waal[2]

1.Department of Neonatology, VU Medical Centre, Amsterdam, The Netherlands
2.Department of Neonatology, John Hunter Hospital, Newcastle NSW and University of Newcastle, NSW, Australia

Keywords
Ductus arteriosus, Newborn, Systematic review

Correspondence
Koert de Waal, Department of Neonatology, John Hunter Hospital, New Lambton, NSW 2305, Australia.
Tel: +61 2 4921 3000 |
Fax: +61 2 4921 4969 |
Email: koert.dewaal@hnehealth.nsw.gov.au

Received
17 May 2011; revised 21 July 2011; accepted 09 September 2011.

DOI:10.1111/j.1651-2227.2011.02468.x

ABSTRACT

Aim: A patent ductus arteriosus (PDA) is associated with morbidity in preterm infants. Treatment is prescribed for a haemodynamically significant duct (HSDA), but its definition varies. We systematically reviewed the clinical and ultrasound criteria used for the definition of an HSDA.

Methods: PubMed and the Cochrane library were searched for randomized trials evaluating ductal treatment. The included studies were explored, and we categorized clinical and ultrasound criteria used to define an HSDA.

Results: Sixty-seven trials were included in our review. Forty-two were placebo-controlled trials, and 25 were comparative trials. The diagnosis of the PDA was made by clinical examination, followed by ultrasound in most trials. Most trials used clinical and ultrasound criteria to define an HSDA, but there was a wide variety in criteria and cut-offs used. Of the clinical criteria, a murmur or hyperdynamic circulation was most used, and of the ultrasound criteria, the left-atrium-to-aorta ratio (LA/Ao ratio) was most used.

Conclusion: We found a wide variety in the definition of an HSDA. This finding implies that comparison of studies is difficult. International consensus should be reached on the definition of an HSDA, which will make future studies more comparable.

Zonnenberg 2012

- Differing ductal sizes were used to define hsPDA
- reversal of flow in various vessels was universally considered severe
- Conclusion: international consensus on the definition of hsPDA is needed to facilitate comparisons across studies

hsPDA

TABLE 1.Hemodynamically Significant Patent Ductus Arteriosus	
Clinical features	Murmur
	Hyperdynamic precordium
	Bounding preductal pulses
	Worsening respiratory status
	Wide pulse pressure
	Hypotension
	Metabolic acidosis
Echocardiographic features	Increased left atrium to aortic root ratio
	Cardiomegaly
	Left-to-right shunting
	Large open ductus
	Reversal of flow in postductal major arteries

Prescott 2016

Kulkarni 2014: Meta-analysis for BNP [=Work in progress]

- All of the studies included infants weighing less than 1500
- 10 BNP studies & 11 NT-proBNP studies were included
- sensitivity 0.88 (95% CI, 0.76-0.95) & a specificity 0.92 (95% CI, 0.81-0.97) for detecting hsPDA as defined by LA:Ao >1.5 and ductal size >1.5 mm
- wide variability between studies
- recommended a composite scoring system to include gestational & chronological age-specific BNP values in addition to clinical parameters

Management of the PDA

وزارة الصحة
Ministry of Health
مدينة الملك فهد الطبية
King Fahad Medical City

Let's first state...

- No RCTs evaluated the effects of tolerating persistent PDAs long term
- All RCTs revealed that while symptoms of hsPDA are reduced by closure of the ductus by any method, long-term benefits have not been demonstrated – NO EXCEPTION!

- Benitz WE. Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis? *J Perinatol*. 2010;30(4):241-252. doi:10.1038/jp.2010.3

Ministry of Health
مدينة الملك فهد الطبية
King Fahad Medical City

Bell and Acarregui

English Español Français Русский | Media | Contact us | Community | My Account

Cochrane

Trusted evidence.
Informed decisions.
Better health.

Search...

Our evidence | About us | Join Cochrane | News and jobs | Cochrane Library ▶

Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants

Fluid Restriction – Cochrane 2014

- 5 RCTs to determine the effects of fluid restriction on neonatal morbidity including PDA
- restricted parenteral fluids are associated with decreased incidence of PDA
- The 5 studies had differing timing, fluid volumes, and restriction durations, leading to confusion about when, how much, and how long fluids should be restricted

Fluid Restriction – De Buyst 2012

- a prospective observational study
- 18 ELBW newborns with hsPDA subjected to fluid restriction from an average of 145 mL/kg/d to an average of 108 mL/ kg/d
- → no beneficial hemodynamic effects, and blood flow decreased in both SVC and SMA

Fluid Restriction – Stephens 2008

- A retrospective study
- 204 ELBW infants receiving high (>170 mL/k/d), medium (135-170 mL/k/d), and low (96-135 mL/k/d) through the first week of life
- demonstrated that only high fluid volumes and only on day 3, but not thereafter, were independently predictive of hsPDA

Lasix

- ‘Furosemide increases prostaglandin production and is therefore counterproductive in the setting of PDA closure’

Brion Luc P, Campbell D. Furosemide for prevention of morbidity in indomethacin-treated infants with patent ductus arteriosus. *Cochrane Database Syst Rev*. 2001;(3). doi:10.1002/14651858. CD001148.

Lasix - Cochrane Review 2001

- Three trials and a total of 70 patients were included
- there was an increase in failure that did not reach statistical significance
- furosemide was contraindicated in dehydrated infants

Lasix - Pacifici 2013: Systematic Review

- "furosemide was not suggested in preterm neonates with hsPDA because of impaired ductal closure in addition to increased creatinine and hyponatremia."

Pacifici GM. Clinical pharmacology of furosemide in neonates: a review. *Pharmaceuticals (Basel)*. 2013;6(9):1094-1129. doi:10.3390/ ph6091094.

COX Inhibitors – Irmesi 2014 Systematic Review

- 88 trials, including more than 15,000 neonates born between 22 and 35 weeks' gestation
- found that both indomethacin and ibuprofen appear comparably effective and both have adverse effects
- ibuprofen's effects appear less severe
- Indomethacin is associated with renal insufficiency, NEC, GI bleeding, GI perforation, alteration in platelet function, and impaired cerebral blood flow
- ibuprofen is associated with PAH, nephrotoxicity, CLD, and ROP

Cox inhibitors – Cochrane 2015

- "ibuprofen is superior to indomethacin, as it was equally as effective at PDA closure but had fewer renal adverse effects and reduced incidence of NEC"
- Oral Ibuprofen > IV Ibuprofen
- Prophylactic indomethacin was associated with reduced hsPDA and IVH but was not associated with improved long-term outcomes (TIPP Trial)
- data are lacking for the long-term effects of ibuprofen, some infants developed persistent PAH after prophylactic ibuprofen

Prophylactic Therapy

- "the reduction in IVH and PDA seen after prophylactic indomethacin therapy has not improved long-term outcomes, hence prophylaxis has fallen out of favor"

Jain A, Shah PS. Diagnosis, Evaluation, and Management of Patent Ductus Arteriosus in Preterm Neonates. *JAMA Pediatr*. 2015;169(9):863-872. doi:10.1001/jamapediatrics.2015.0987.

Paracetamol – Also a COX inhibitor (*In high dose)

- Advantage of no peripheral vasoconstrictive effects
- In low concentrations, stimulates PG synthesis
- in high concentrations, inhibits PG synthesis

Paracetamol – Cochrane 2015

- 2 trials comprising 250 infants
- compared oral paracetamol with oral ibuprofen
- similar PDA closure rates and fewer adverse effects in the paracetamol groups
- “animal studies indicated adverse neurodevelopmental effects of paracetamol; so, long-term outcome studies are needed before it can be recommended”

Ligation

- Reserved for refractory ductus
- In 2013, Tashiro reviewed 63,000 patients in the Kid's Inpatient Database, for outcomes associated with surgical ligation
- Findings indicated that infants requiring surgical ligation were less stable and had more comorbidities such as renal failure, NEC, and coagulopathy, lending credence to the indication bias theory.

Trans-Catheter Closure

- For infants older than 6 months or weighing more than 6 kg who demonstrate LV volume overload and PAH
- Asymptomatic patients are also treated to avoid PAH and endocarditis
- The stiffness of the delivery sheath limit this approach in infants with low body weight

Baruteau A-E, Hascoët S, Baruteau J, et al. Transcatheter closure of patent ductus arteriosus: past, present and future. *Arch Cardiovasc Dis*. 2014;107(2):122-132. doi:10.1016/j.acvd.2014.01.008

Clinical Implications

- "it seems prudent for the practitioner to limit fluids as much as possible while preserving adequate hydration, nutrition, and SVC and SMA blood flow."

Prescott 2016

وزارة الصحة
Ministry of Health
مدينة الملك فهد الطبية
King Fahad Medical City

Why do we care to treat early

- Physiologic Reason: Less response after 2 wk
- Human Reason: We like to treat things

وزارة الصحة
Ministry of Health
مدينة الملك فهد الطبية
King Fahad Medical City

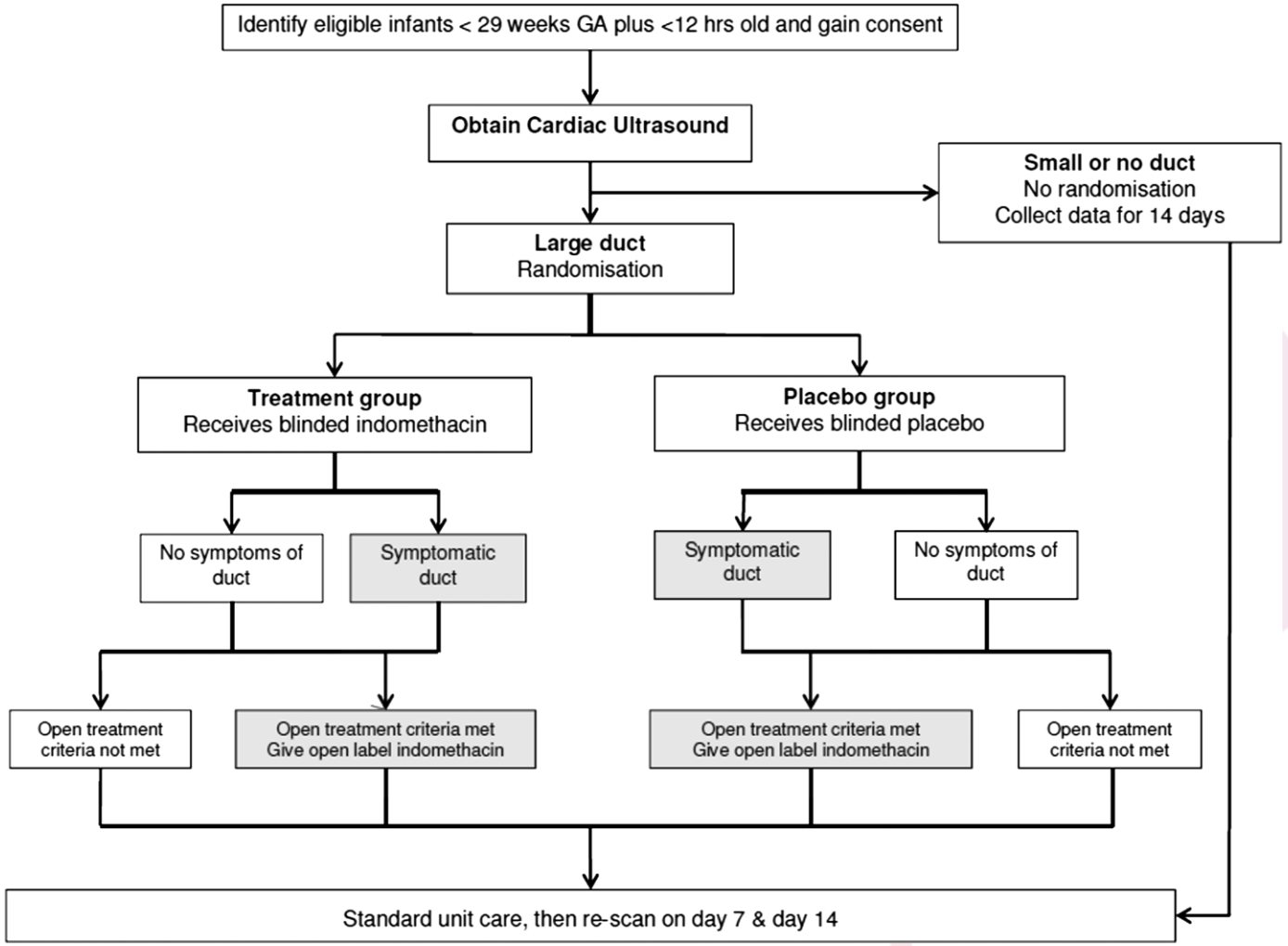
Kluckow 2016

Original article

A randomised placebo-controlled trial of early treatment of the patent ductus arteriosus

Martin Kluckow,[1,2] Michele Jeffery,[1] Andy Gill,[3] Nick Evans[2,4]

Kluckow 2016



Kluckow 2016

Table 2 Outcomes of infants with a large patent ductus arteriosus (PDA) randomised to indomethacin or placebo

	Indomethacin	Placebo	p Value
N	44	48	
Primary outcome (death/ abnormal cranial ultrasound)	8 (18%)	9 (19%)	1.0
Died	4 (9%)	5 (10%)	1.0
PIVH Grade 2–4	2 (4.5%)	6 (12.5%)	0.21
PVL/Cysts/Dilation	4 (9%)	4 (8%)	1.0
GA stratification primary outcome			
23–24 weeks	3/8	3/8	1.0
25–26 weeks	3/15	5/16	0.69
27–28 weeks	2/21	1/24	0.59

GA, gestational age; PIVH, periventricular/intraventricular haemorrhage; PVL, periventricular leukomalacia.

وزارة الصحة
Ministry of Health
مدينة الملك فهد الطبية
King Fahad Medical City

Conclusions Early cardiac ultrasound-targeted treatment of a large PDA is feasible and safe, resulted in a reduction in early pulmonary haemorrhage and later medical treatment but had no effect on the primary outcome of death or abnormal cranial ultrasound.

وزارة الصحة
Ministry of Health
مدينة الملك فهد الطبية
King Fahad Medical City

The intensity of the conviction that a hypothesis is true has no bearing on whether it is true or not.

Sir Peter Medawar

1915-1987

PDA-TOLERATE Study 2018

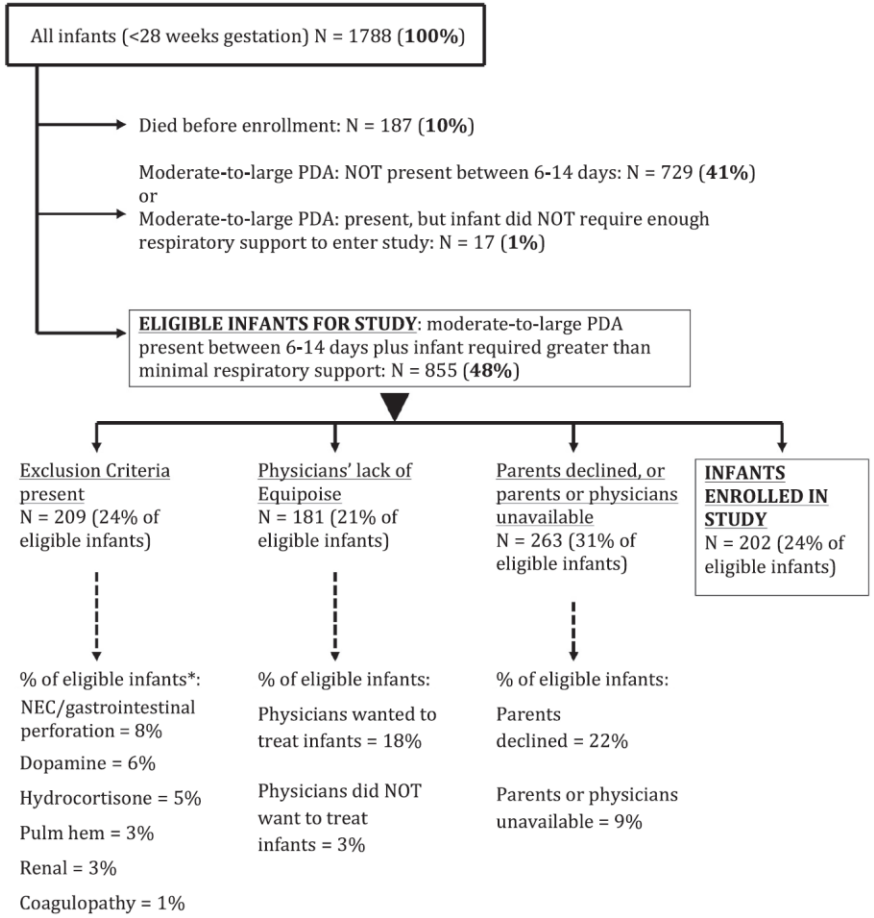
THE JOURNAL OF PEDIATRICS • www.jpeds.com

ORIGINAL ARTICLES

PDA-TOLERATE Trial: An Exploratory Randomized Controlled Trial of Treatment of Moderate-to-Large Patent Ductus Arteriosus at 1 Week of Age

Ronald I. Clyman, MD[1,2], Melissa Liebowitz, MD[1], Joseph Kaempf, MD[3], Omer Erdeve, MD[4], Ali Bulbul, MD[5], Stellan Håkansson, MD[6], Johanna Lindqvist, MD[6], Aijaz Farooqi, MD[6], Anup Katheria, MD[7], Jason Sauberan, PharmD[7], Jaideep Singh, MD[8], Kelly Nelson, MD[8], Andrea Wickremasinghe, MD[9], Lawrence Dong, MD[9], Denise C. Hassinger, MD[10], Susan W. Aucott, MD[11], Madoka Hayashi, MD[11], Anne Marie Heuchan, MD[12], William A. Carey, MD[13], Matthew Derrick, MD[14], Erika Fernandez, MD[15], Meera Sankar, MD[16], Tina Leone, MD[17], Jorge Perez, MD[18], Arturo Serize, PA[18] and the PDA-TOLERATE (PDA: TO LEave it alone or Respond And Treat Early) Trial Investigators*

PDA-TOLERATE 2018



PDA-TOLERATE 2018

Table IV. Neonatal outcomes

Outcomes	CT group (n = 98)	ERT group (n = 104)	Risk ratio (95% CI)	Risk difference (95% CI)
Primary outcome				
Ligation or outpatient PDA follow-up, %	39	32	0.81 (0.55-1.2)	−7 (−21 to 6)
PDA ligation, %	12	12	1.00 (0.47-2.1)	0 (−9 to 9)
Outpatient PDA follow-up, %	27	19	0.72 (0.42-1.2)	−7 (−19 to 4)
Secondary outcomes				
NEC, %*	19	16	0.82 (0.44-1.5)	−3 (−14 to 7)
BPD, %	53	49	0.94 (0.70-1.3)	−3 (−18 to 11)
BPD or death before 36 wk, %	57	58	1.00 (0.80-1.3)	1 (13-14)
Death at any time during hospitalization, %	10	19§	1.90 (0.92-3.8)	9 (−1 to 19)
PDA (moderate/large) at 10 d after randomization, %*	80	41‡	0.51 (0.40-0.66)	−39 (−51 to −26)
Rescue criteria met, %	62	31‡	0.49 (0.35-0.69)	−32 (−45 to −18)
Received rescue treatment, %	48	18‡	0.38 (0.24-0.60)	−30 (−43 to 18)
Received furosemide ≥14 d, %*	46	35§	0.75 (0.54-1.1)	−11 (−24 to 2)
Days until enteral intake 120 mL/kg/d, median (IQR)*	12 (5-24)	16 (7.5-23)	Mean difference, 1.4 (1.3-1.5)¶	
Daily weight gain, g/kg, mean ± SD*	22.8 ± 4.6	22.5 ± 4.8	Mean difference, 0.25 (−1.1 to 1.7)¶	
Days until last gavage feeding, median (IQR)*	80 (61-97)	76 (66-104)	Mean difference, 1.0 (1.0-1.1)¶	
Other exploratory analyses				
Pulmonary hemorrhage, %*	2.0	1.9	0.94 (0.14-6.60)	0 (−4 to 4)
sIVH, %	11.2	18.3	1.10 (0.43-2.6)	1 (−7 to 8)
PVL (cystic), %	11	13	1.10 (0.52-2.3)	1 (−8 to 10)
ROP (treated), %	16	18	1.20 (0.61-2.3)	3 (−9 to 14)
Pneumonia,%*	9	8	0.84 (0.34-2.1)	−2 (−9 to 6)
Bacteremia, %*	21	30	1.40 (0.86-2.3)	8 (−4 to 20)
Bacteremia, CONS, %*	4	4	0.94 (0.24-3.7)	0 (−6 to 5)
Bacteremia, non-CONS, %*	17	26	1.50 (0.87-2.6)	9 (−3 to 20)
Received dopamine for ≥3 d, %*	25	13.3†	0.53 (0.29-0.98)	−12 (−23 to −1)
Received corticosteroids for ≥7 d, %*	38	28	0.74 (0.49-1.1)	−10 (−23 to 3)
Days until discharge, median (IQR)*	93 (73-109)	92 (76-120)	Mean difference, 1.0 (1.0-1.2)¶	

PDA-TOLERATE 2018

Table I. Rescue criteria present when infants initially qualified for having met rescue criteria

Criteria present when infants initially met the rescue criteria*	CT group,* %	ERT group,* %
Moderate-to-large PDA on echocardiogram, plus	100	100
Inotrope-dependent hypotension	30	20
Oliguria	0	0
Nipple feeding and work of breathing	2	3
Respiratory	95	93

Respiratory support needed	FiO_2 needed	At postnatal age, d		
Intubated	>0.30	>15	33	47
Intubated	≤0.30	>20	47	27
Nasal CPAP or nasal ventilation	>0.30	>20	7	13
Nasal CPAP or nasal ventilation	0.25-0.30	>30	3	0
Nasal CPAP or nasal ventilation	<0.25	>45	5	6

Conclusions In preterm infants age <28 weeks with moderate-to-large PDAs who were receiving respiratory support after the first week, ERT did not reduce PDA ligations or the presence of a PDA at discharge and did not improve any of the prespecified secondary outcomes, but delayed full feeding and was associated with higher rates of late-onset sepsis and death in infants born at ≥26 weeks of gestation. *(J Pediatr 2018;■■:■■-■■).*

وزارة الصحة
Ministry of Health
مدينة الملك فهد الطبية
King Fahad Medical City

Take Home Messages

- PDA is an association and not necessarily a causation
- Avoiding liberal fluid intake may help close PDA
- Oral Ibuprofen seems to be the best overall agent for closure
- Avoid Furosemide
- Early treatment (1-2 weeks) unlikely to improve outcomes
- Conservative treatment is a feasible and safe option
- Further trials are needed for more conservative management

وزارة الصحة
Ministry of Health
مدينة الملك فهد الطبية
King Fahad Medical City

Thank you

Questions?

وزارة الصحة
Ministry of Health
مدينة الملك فهد الطبية
King Fahad Medical City

EBNEO

Evidence-Based Neonatology

Please follow on Twitter:
@oelkhateeb @EBNEO

ebneo.org